

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

Foreign Patent Branch Examiner's Request Form

EXAMINER Chih-Hsin Kam
ART UNIT 1653
PHONE 308-9437
CASE NO 09/866,033

PROCESSOR _____
DATE ASSIGNED _____
DATE FILLED _____

FILE COPY

COUNTRY <u>AU</u>	DOCUMENT <u>549024</u>	PAGES <u>all 24 pgs</u>
COUNTRY _____	DOCUMENT _____	PAGES _____
COUNTRY _____	DOCUMENT _____	PAGES _____
COUNTRY _____	DOCUMENT _____	PAGES _____
COUNTRY _____	DOCUMENT _____	PAGES _____
COUNTRY _____	DOCUMENT _____	PAGES _____
COUNTRY _____	DOCUMENT _____	PAGES _____
COUNTRY _____	DOCUMENT _____	PAGES _____
COUNTRY _____	DOCUMENT _____	PAGES _____
COUNTRY _____	DOCUMENT _____	PAGES _____
COUNTRY _____	DOCUMENT _____	PAGES _____
COUNTRY _____	DOCUMENT _____	PAGES _____
COUNTRY _____	DOCUMENT _____	PAGES _____
COUNTRY _____	DOCUMENT _____	PAGES _____
COUNTRY _____	DOCUMENT _____	PAGES _____
COUNTRY _____	DOCUMENT _____	PAGES _____

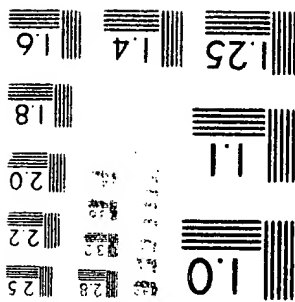
COMPLETED

RECEIVED
SCIENTIFIC & TECHNICAL
INFORMATION CENTER
OCT 29 AM 1:12
PAT. & TM. OFFICE

Foreign Document Division: Scientific and Technical Information Center CP 3/4 Room 2C01.
Telephone: 308-1076 Fax: 308-1000

Please send the reference to
CM1, 9B-01 . Thanks

3



COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

APPLICATION FOR A STANDARD PATENT

549024

X
We EFAMOL LIMITED, of 71/74 Mark Lane,
LONDON, E.C.3, England,

hereby apply for the grant of a Standard Patent for an invention entitled

"TREATMENT OF SCHIZOPHRENIA"

which is described in the accompanying ^{provisional} ~~complete~~ specification

Details of basic application(s)

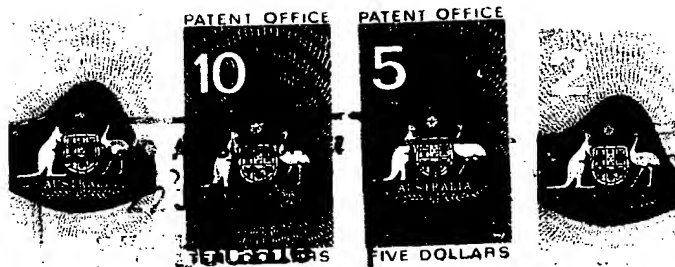
~~XXXXXXXXXX~~

~~XXXXXXXXXXXXXXXXXXXX~~

~~XXXX~~

Number of original application: 43551/79

Person by whom made: EFAMOL LIMITED



The address for service is care of DAVIES & COLLISON, Patent Attorneys, of 1 Little Collins Street, Melbourne, in the State of Victoria, Commonwealth of Australia

Dated this 18th day of January, 1982.

H. W. Rimington

1. THE COMMISSIONER OF PATENTS

a member of the firm of DAVIES & COLLISON for and on behalf of the Applicant

62

Davies & Collison, Melbourne and Canberra

DAVIES & COLLISON, MELBOURNE and CANBERRA.

(12) AUSTRALIAN PATENT ABRIDGMENT
(19) AU

(11) AU-B-79776/82

(54) TREATING SCHIZOPHRENIA WITH BETA LACTAMS

(71) EFAMOL LIMITED

(21) 79776/82

549024

(22) 22.1.82

(24) 23.1.78

(43) 22.4.82

(44) 9.1.86

(51)3 A61K 31/545 A61K 31/43

(62) 43551/79

(72) DAVID FREDERICK HORROBIN

(74) DM

(57) Beta lactam antibiotics are believed to enhance the utilisation of dihomogamma-linolenic ester reserves and hence the biosynthesis of prostaglandins of the 2 series.

Claim 1. A method of treating schizophrenia resulting from 1- series/
2-series PG imbalance wherein an effective amount of a β -lactam
antibiotic is administered to a patient to ameliorate said imbalance.

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

COMPLETE SPECIFICATION

(Original)

FOR OFFICE USE

797 76 /82

549024

Class

Int. Class

Application Number: 79-6
Lodged:

Complete Specification Lodged:
Accepted:
Published:

Priority:

Related Art:

This document contains the
amendments made under
Section 49.

and is correct for printing

Name of Applicant: EFAMOL LIMITED

Address of Applicant: 71/74 Mark Lane, LONDON, E.C.3, England

Actual Inventor(s): DAVID FREDERICK HORROBIN

Address for Service: DAVIES & COLLISON, Patent Attorneys,
1 Little Collins Street, Melbourne, 3000.

Complete specification for the invention entitled:

"TREATMENT OF SCHIZOPHRENIA"

The following statement is a full description of this invention,
including the best method of performing it known to us :-

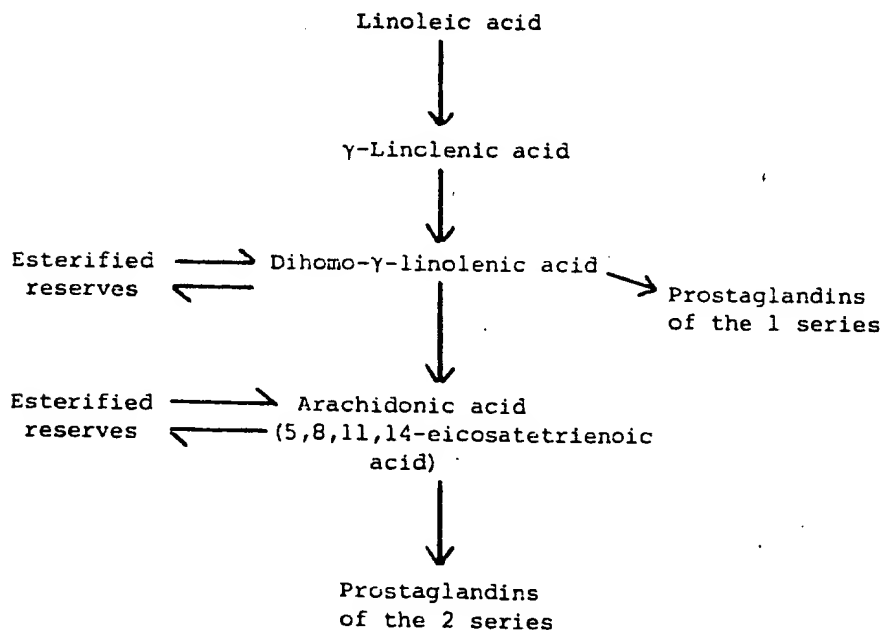
FIELD OF THE INVENTION

This invention relates to the treatment of schizophrenia.

GENERAL BACKGROUND

Considerable interest has been shown in recent years in the
5 use of prostaglandin (PG) precursors in medicine.

For various reasons it is not practical to administer
naturally-occurring prostaglandins such as PGE 1 and PGE 2 to
patients. Consequently, considerable attention has focussed on
the use of prostaglandin precursors including linoleic acid
10 (9,12-octadecadienoic acid), γ -linolenic acid (6,9,12-octadecatrienoic
acid) and dihomo- γ -linolenic acid (5,8,11-eicosatrienoic acid),
conversion in the body being believed to be as follows:



Thus γ -linolenic acid and dihomogamma-linolenic acid function as precursors for both 1- and 2-series PG's. The present inventor believes it advantageous if the biosynthesis of 1-series PG's can be effected preferentially to that of 2-series PG's in conditions
5 in which 1-series PG imbalances or lack need to be corrected.

It has previously been believed that selective enhancement of 1-series PG formation and inhibition of 2-series PG formation are impossible because the mobilisation of DGLA reserves and the mobilisation of AA reserves have been thought to be the same reaction,
10 mediated by the same phospholipase. Similarly the formation of 1-series endoperoxides from DGLA, leading to 1-series PG's has been thought inseparable from the formation of 2-series endoperoxides from AA, leading to 2-series PG's. The inventor however has evidence that these assumptions are not true and that agents may
15 be found which regulate the reactions selectively; for example penicillin and zinc appear to activate DGLA mobilisation without effecting AA mobilisation and the formation of 1-series PG's is increased preferentially.

Most broadly, agents effective are those which:

- 20 (a) selectively activate DGLA mobilisation or conversion to endoperoxides, with small or no effect on AA mobilisation or conversion;
(b) inhibit conversion of DGLA to AA. (The body can make up any lack of AA from reserves to maintain 2-series PG production if required);
(c) selectively inhibit AA mobilisation or conversion to
25 endoperoxides, with small or no effect on DGLA mobilisation or

conversion.

Materials influencing the 1-series/2-series PG balance in the body, in favour of 1-series PG's, which may be referred to as '1-series PG enhancers', are thus believed to act by one or
5 more of the above mechanisms.

THE INVENTION

Thus at its broadest the present invention provides a method of treating schizophrenia in which a β -lactam antibiotic is administered, to influence the 1-series/2-series PG balance
10 in the body in favour of 1-series PG's.

DESCRIPTION OF THE PRIOR ART

Prior art within this general area includes the following patents and papers.

- (i) U.S. Patents Nos. 3 993 775 (issued November 23rd, 1976) and
15 4 058 594 (issued November 15th, 1977) of John Williams, which described a method of providing an immuno-suppressive effect in a patient undergoing organ or tissue transplant or suffering from multiple sclerosis comprising administration of a daily dosage of from 5 mg to 3 g of γ -linolenic acid or dihomogamma-linolenic acid
20 or a functional derivative thereof.
- (ii) British Patent Specification No. 1 082 624, published September 6th, 1967, (Calmic Limited), which discloses effectiveness of γ -linolenic acid in the treatment of vascular diseases.
- (iii) McCormack, Neil and Sim (The Lancet, page 508, September 3rd,
25 1977), who described preliminary work on the use of an oil containing

a mixture of linoleic acid and γ -linolenic acid (as triglycerides) in the treatment of rheumatoid arthritis.

(iv) Sim and McCraw (Thrombosis Research Volume 10, pages 385-397, 1977), who describe activity of the methyl esters of γ -linolenic acid and dihomogamma-linolenic acid in vitro and in vivo on blood platelet function in non-human primates and in man.

SCHIZOPHRENIA

In the Lancet, page 936, April 30, 1977 the present inventor has suggested that schizophrenia is a prostaglandin deficiency disease. Schizophrenia is not a disorder which would suggest the use of immuno-suppressive drugs. The specific suggestion was made that arachidonic acid, known to be a precursor of prostaglandins of the 2-series should alleviate schizophrenia.

As a result of further research, the present inventor now believes that schizophrenia is due not to a deficiency of 2-series PGs but rather to a deficiency of PGE 1 and other PGs of the 1-series, of which arachidonic acid is not a precursor, or an imbalance in the normal ratio of 1-series and 2-series PGs.

Further it has been surprisingly found that β -lactam antibiotics, for example phenoxymethyl penicillin (penicillin V), are able to stimulate the production of PGs of the 1-series in rats, and moreover that the use of such compounds in



the treatment of patients suffering from "classic" schizophrenia has indicated that they have an antipsychotic activity.

Thus the invention provides a method of treating schizophrenia in a patient which comprises administering an effective amount
5 of a β -lactam antibiotic.

β -lactam antibiotics which may be used according to the present invention, are conveniently any of the known penicillin and cephalosporin antibiotics (including semi-synthetic antibiotics) such as, for example, penicillin G, penicillin N, penicillin V,
10 cephalixin, cephalothin, ampicillin, amoxycillin, cloxacillin and cephaloglycin. Any of these may be used in the form of their physiologically functional non-toxic derivatives, for example alkali metal salts e.g. sodium and potassium salts, and salts with organic bases, and reference to an antibiotic herein (including the claims)
15 includes reference to such derivatives.

The antibiotics may for example be administered orally, parenterally or rectally as desired.

The antibiotic is preferably administered in the form of dosage units. Suitable daily dosages of said active ingredient
20 may for example be in the range 0.5 to 3.0 g per day in patients of average weight. Such daily dosages may conveniently be divided into for example, two, three or four equal doses to be administered two, three or four times daily respectively.

In severely disturbed patients it may be desirable to
25 additionally administer conventional tranquillizers in addition to

regular treatment with penicillin, but this is only required when such patients experience extreme agitation, insomnia or hallucinations.

5 The use of penicillins in the long term treatment of schizophrenia is especially desirable in view of the known relative absence of side effects of these drugs. Thus, penicillin has been administered for many years to patients having rheumatic heart disease in order to prevent streptococcal infections, and there is virtually no evidence of long term toxicity.

10 Care should of course be taken to ensure that the patient is not allergic to the drug of choice. With respect to the known ability of penicillins to produce reactions in some patients due to penicillin hypersensitivity, there is evidence to suggest that schizophrenics have a reduced incidence of allergic reactions and
15 more particularly of penicillin hypersensitivity. Thus, the problem, usually associated with penicillin antibiotic therapy, of hypersensitization in a small number of patients, is not quite so important in the treatment of schizophrenia using penicillins.

20 A valuable benefit of the present invention is that the hitherto extensively used chemotherapeutic agents for schizophrenia have been associated with a tranquillizing activity, with the result that the use of these drugs in therapy is combined with an often undesired heavy sedation of the patient. Also such drugs may be responsible for the production of irreversible damage in
25 up to 70% of patients to those parts of the brain which control

movement. Avoidance or substantial avoidance of the use of these drugs is thus of great value.

It is of particular value to combine the above two new approaches in a method of treating schizophrenia in a patient which comprises administering to the patient an effective amount of a β -lactam antibiotic together with γ -linolenic acid and/of dihomogamma-linolenic acid, said acids being used, if desired, as physiologically functional derivatives thereof, and if desired in association with linoleic acid or other fat acids.

β -lactam antibiotics which may be used are conveniently as above.

The dosages also are suitably as above, in conjunction with suitable amounts of γ -linolenic acid, dihomogamma-linolenic acid or equivalent derivative, in particular 0.1 to 1.0 g daily.

If it is not desired to have compositions comprising both the antibiotics and the γ -linolenic or other acid or derivatives, packs may be prepared comprising the active materials presented for separate administration in the appropriate relative amounts, and such packs are within the purview of the invention.

DIETARY COMPOSITIONS

The invention is chiefly described in terms of pharmaceutical compositions, but it will be understood that the γ -linolenic and other acids, being in the nature of dietary supplements, could if available at an economic price be incorporated in a dietary margarine or other foodstuff; such foodstuffs are referred to

herein as dietary compositions.

FORMS AND SOURCES OF γ -LINOLENIC AND OTHER ACIDS

Convenient physiologically functional derivatives of γ -linolenic acid and dihomoc- γ -linolenic acid include the C₁-C₄ alkyl (e.g. methyl and ethyl) esters and the glycerides of the acids.

If desired, pharmaceutical compositions may be produced by associating natural or synthetic γ -linolenic acid (or a physiologically functional derivative thereof) and/or dihomoc- γ -linolenic acid (or a physiologically functional derivative thereof) as such, with an acceptable pharmaceutical vehicle. It will however generally be convenient to incorporate the γ -linolenic acid into compositions in the form of an available oil having a high γ -linolenic acid content.

At the present time known natural sources of oils having a high γ -linolenic acid content are few (there are no known natural sources of significant amounts of dihomoc- γ -linolenic acid). One source of oils currently available is the seed of Evening Primrose species such as Oenothera biennis L. and Oenothera lamarckiana, the oil extract therefrom containing γ -linolenic



acid and linoleic acid in the form of their glycerides together with other glycerides. Another source of γ -linolenic acid is the seed of Borage species such as Borago officinalis which, though its current yield per acre is low, provides a richer source of γ -linolenic acid than Oenothera oil. Recent studies on fungi which can be cultivated by fermentation promise a fungal oil source.

The seed oil extracts referred to above can be used as such or can if desired be fractionated to yield an oily composition containing the triglycerides of γ -linolenic acid and linoleic acid as the only fatty acid components, the γ -linolenic acid content being a major proportion. Seed oil extracts appear to have a stabilising effect upon any dihomogamma-linolenic acid or physiologically functional derivative thereof incorporated therein.

USE OF ZINC

As has been mentioned above, γ -linolenic acid and dihomogamma-linolenic acid function as precursors for both 1 and 2-series PG's. The present inventor believes it advantageous if the biosynthesis of 1-series PG's can be effected preferentially to that of 2-series PG's in conditions, not merely schizophrenia in which 1-series PG imbalances or lack need to be corrected.

Without restriction to the theory, the present inventor believes that zinc tends to stimulate the biosynthesis of 1-series PG's and specifically that it potentiates mobilisation of esterified reserves of dihomogamma-linolenic acid. This enables one to use zinc conjointly with γ -linolenic acid and/or dihomogamma-linolenic acid.

USE OF β -LACTAM ANTIBIOTICS

The present inventor believes that the reason for the effectiveness



of the antibiotics is that, as he believes with zinc, they enhance utilisation of ester reserves of dihomog- γ -linolenic acid.

Whether or not this is so, and no restriction to the theory is intended, zinc and antibiotics do appear to have parallel effects in treating schizophrenia when used with the γ -linolenic or other acids and derivatives.

It is also, further possible and has been found valuable to use both zinc and β -lactam antibiotics conjointly with the γ -linolenic acid, dihomog- γ -linolenic acid or derivatives as described earlier.

In all cases the amounts of active materials are as discussed already and association of the γ -linolenic acid with linoleic or other fat acids is possible.

PHARMACEUTICAL PRESENTATION

The compositions according to the invention are conveniently in a form suitable for oral, rectal, parenteral or topical administration in a suitable pharmaceutical vehicle, as discussed in detail for example in U.K. Patent Specification No. 1 082 624 and in any case known generally according to the type of preparation. Thus for example tablets, capsules, ingestible liquid or powder preparations, creams and lotions for topical application, or suppositories, can be prepared as required.

Advantageously a preservative such as α -tocopherol is incorporated into the preparations. α -Tocopherol in a concentration of about 0.1% by weight has been found suitable for the purpose.

It will be understood that the absolute quantity of active ingredients present in any dosage unit should not exceed that appropriate to the rate and manner of administration to be employed but on the other hand should also desirably be adequate to allow
5 the desired rate of administration to be achieved by a small number of doses. The rate of administration will moreover depend on the precise pharmacological action desired.

The following Examples serve to illustrate pharmaceutical compositions according to the invention:-

10

EXAMPLES

Pharmaceutical compositions containing a unit dose of an oil extract from the seeds of Oenothera biennis L. optionally with methyl dihomog- γ -linolenate and/or zinc sulphate and/or penicillin V are prepared by encapsulation of the natural oil in soft gelatin
15 capsules manufactured by known methods.

The oil is extracted from the seeds by one of the conventional methods of extraction such as cold pressure, screw pressure after partially cooking the seed, or solvent extraction.

Fractionation of a typical sample of this oil shows a yield
20 of 97.0% oil in the form of methyl esters, with the relative proportions:

Palmitate	6.15
Stearate	1.6
Oleate	10.15
25 Linoleate	72.6
γ -Linolenate	8.9



As preservative, α -tocopherol is added to the oil in concentration of 0.1%.

Gelatin capsules containing oil extracts prepared as described above, each having the following contents of active ingredients (0.5 g oil extract = ca 0.045 g γ -linolenic acid), are prepared in conventional fashion. The zinc may conveniently be incorporated as zinc oleate made by the method disclosed in Monatschrift 42 287 (1921) and similar methods may be applied to make for example zinc γ -linclenate if desired.

10

EXAMPLES, SCHIZOPHRENIA

EXAMPLE 1

Oil extract	0.5 g
Penicillin V	0.25 g

Two capsules may be administered thrice daily in the treatment of schizophrenia.

15

EXAMPLE 2

Oil extract	0.5 g
Penicillin V	0.25 g
Zinc sulphate	10 mg

Two capsules may be administered thrice daily in the treatment of schizophrenia.

20

EXAMPLE 3

Oil extract	0.5 g
Methyl dihomog- γ -linolenate	10 mg
Penicillin V	0.25 g
Zinc sulphate	10 mg

25

Two capsules may be administered thrice daily in the treatment of schizophrenia.

EXAMPLE 4

Penicillin V tablets 250 mg made by conventional methods
5 may be administered in the treatment of schizophrenia, one tablet four times a day.

EVIDENCE OF EFFICACY

The conditions are considered in turn.

SCHIZOPHRENIA

10 1. Penicillin alone

A group of ten severe chronic schizophrenics stabilised on standard phenothiazine drug therapy and known to relapse without it were taken off these drugs and given penicillin V 300 mg four times a day, rising to 600 mg. In nine out of the ten cases the
15 stabilised condition was successfully maintained on the penicillin alone over many weeks, with benefit to the patients from the absence of the known phenothiazine side effects including sleepiness. One patient reacted adversely to the higher doses of penicillin and was returned to the previous therapy.

20 Further, a female patient aged 50 who had suffered for 20 years from severe schizophrenia and was aggressive, paranoid and hypochondriacal in spite of conventional drug treatment with haloperidol (10 mg tds) plus flupenthixol decanoate (40 mg/month), was taken off these drugs. After three weeks she was given
25 penicillin V 250 mg qds. In the first week her symptoms became



less severe and a steady improvement was maintained over five months.

2. Oenothera oil alone

Three further patients stabilised on standard phenothiazine drug therapy were taken off these drugs and instead given Oenothera oil 2 x 0.6 ml capsules qds. The stabilised condition of each patient was maintained for several weeks.

3. Oenothera oil and penicillin together

The female patient referred to above was taken off the penicillin and after three weeks had again become markedly aggressive, paranoid and hypochondriacal. She was then given Oenothera oil (2 x 0.6 ml capsules qds) and penicillin V (250 mg qds). There was some initial nausea and headache but after two weeks hypochondriacal delusions ceased and after six weeks paranoid delusions, aggressiveness and incongruity of affect had also disappeared. Further, 6 kg in weight were lost in the course of 16 weeks in spite of a regular diet.

A further, male patient of 31 had suffered from severe schizophrenic illness for 12 years and had been an in-patient for 7 years, aggressive, hearing voices, of wild staring appearance and not speaking spontaneously to others. He had been receiving fluphenazinedecanoate 75 mg every two weeks, benzhexol 5 mg three times a day and supplementary chlorpromazine as required. He was taken off these drugs and given Oenothera oil and penicillin as above for one month and an increase to 3 capsules qds in the oil thereafter. Over a period of six months he became co-operative, not easily upset

by fellow patients, without aggressions, speaking spontaneously and appropriately to others, and with almost normal affect. His BPRS score dropped from 44 to 21 over the period.

Four other severe chronic schizophrenics controlled by phenothiazines were withdrawn from them and given the Oenothera oil and penicillin. The condition of each was maintained without the side effects of the other drugs.

4. Oenothera oil, penicillin and zinc

Preliminary trials with a small group of similar patients to those in the previous trials have been promising on the following

Oenothera oil 6 or 8 x 0.6 ml capsules/day

Penicillin 250 mg qds

Zinc, as sulphate 20 to 40 mg/day

USE OF ZINC

Substantial clinical results are not at present available on the use of zinc but the present inventor believes, without wishing to be limited to the theory, that at the root of all the conditions lies a fault in prostaglandin metabolism whereby PG's of the 1-series are lacking or their balance with 2-series PG's is upset. From evidence such as that listed below the inventor believes that zinc increases formation of 1-series PG's selectively, apparently by mediating the mobilisation from ester resources of dihomog- γ -linolenic acid.

Thus zinc is indicated herein, as favouring 1-series PG synthesis specifically from administered γ -linolenic acid and



related materials.

In one group of experiments the test preparation was the isolated superior mesenteric vascular bed, taken from male rats as for example described in the Canadian J. Physiol Pharmacol 54:357, 1976. The perfusion flow rate was at a constant value between 3 to 4 ml/min., pressure 25 to 30 mm Hg, using Krebs bicarbonate buffer containing in mM 150 Na, 4.0 K, 1.0 Mg, 2.5 Ca, 1.7 phosphate, 25 bicarbonate and 11.1 glucose.

Prior to testing the basic vasoconstrictive effect of norepinephrine, as the bitartrate, in successive 10 ng amounts was established, as the amplitude of a transient rise of about 1 min in the perfusion pressure.

Zinc, as the chloride, was then added to the perfusion buffer at successive concentrations and the norepinephrine response measured after 15 minutes at each.

The following results were obtained:

Zinc concentration (μ g/ml)	Response as % of basic level
0.1	112
0.2	115
0.4	130
0.8	138

In the presence of 50 μ g/ml of indomethacin, a known blocking agent for PG synthesis, used with 10 ng/ml PGE 2 to give apparently normal vascular reactivity, the zinc had no effect on the

norepinephrine response.

Similar tests with dihomog- γ -linolenic acid and PGE 1 gave
respective rises up to a maximum of 130% of the basic response
at 50 ng/ml of the acid and a maximum of 150% of the basic response
5 at 2.8×10^{-11} M PG.

The results show that zinc gives responses like those of
dihomog- γ -linolenic acid and of PGE 1, responses moreover which are
not given when PG synthesis is blocked and PGE 1 supplied, and
thus that conditions treated with γ -linolenic acid (and thus
10 effectively with dihomog- γ -linolenic acid) may be enhanced in the
direction of 1 series PG synthesis by the addition of zinc.

USE OF ANTIBIOTICS

On tests carried out as above, both penicillin V and
penicillin G have given responses similar in kind and degree to
15 those given for zinc, supporting further inventor's belief that
 β -lactam antibiotics are of value in the treatment of schizophrenia
in similar way to the action of zinc and as evidenced in the
results with schizophrenia.

20

25

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method of treating schizophrenia resulting from 1- series/
2-series PG imbalance wherein an effective amount of a β -lactam
antibiotic is administered to a patient to ameliorate said imbalance.
2. A method according to claim 1 wherein the antibiotic is a
5 natural or semi-synthetic penicillin or cephalosporin antibiotic.
3. A method according to claim 2, wherein the antibiotic is
selected from penicillin G, penicillin N, penicillin V, cephalothin,
ampicillin, amoxycillin, cloxacillin, cephalixin and cephaloglycin.
4. A method according to any preceding claim, wherein the
10 amount of antibiotic is 0.5 to 3.0 g/day.
5. A method according to any preceding claim, wherein
conventional tranquillisers are administered with the antibiotic.

DATED this 29th day of October, 1985

15 **EFAMOL LIMITED**

by its Patent Attorneys

DAVIES & COLLISON

